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By V. I. Levenson

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AN AUTORADIOGRAPHIC STUDY OF THE PROCESS OF HORMONE FORMATION IN THE THYROID GLAND UNDER VARIOUS EXPERIMENTAL CONDITIONS [1]

[Following is the translation of an article by V. I. Levenson entitled "Autoradiograficheskoye izucheniye protsessa gormonoobrazovaniya v shchitovidnoy zheleze v razlichnykh eksperimental'nykh usloviyakh" (English version above) in Arkhiv Patologii, Vol. 22, No. 4, 1960, Moscow, pages 34-42.]

From the Chair of Pathological Anatomy (Head -- Corresponding Member of the Academy of Medical Sciences, Professor A. I. Strukov) of the First Moscow Order of Lenin Medical Institute imeni I. M. Sechenov.

(Submitted 9 April 1959.)

In the study of the problem of the functional morphology of the thyrod gland, a great amount of factual material has been obtained as the result of the investigation of the histological structure of the tissue, the cellular organoids and the staining properties of the colloid. However, the use of these data for the evaluation of the hormone forming activity of the thyroid gland encounters considerable difficulties. The practical experience of biopsy investigations shows that the conduct of clinical-anatomical comparisons on the basis of the histological characterization of the thyroid tissue often proves to be impossible (B. N. Mogil'nitskiy, Selzer, and others.) The absence of specific methods of detecting the thyroid hormone has caused the histophysiological conclusions based on morphological investigations to be quite contradictory.

The use of radioactive iodine and the working out of autoradiographic methods of investigation (Hamilton, Leblond with co-workers; Doniach and Pelc, 1950; Ya. V. Mamul',

[1] Delivered at the session of the Moscow Society of Pathological Anatomists 20 March 1959.

1952, and others) has opened wide possibilities of the functional-morphological investigation of the thyroid gland on the basis of the determination in the tissue of organic compounds of iodine, the metabolism of which is closely associated with the process of hormone formation. The theoretical bases and the technique of autoradiography have been set forth in detail in [published] works (Boyd, Fitzgerald, Ya. V. Mamul', 1955, G. S. Lykova and others.)

The object of the present investigation was: 1) the autoradiographic study of the process of hormone formation in the normal thyroid gland; 2) the study of the process of hormone formation under conditions of disturbance of the function of the thyroid gland; 3) the comparison of the data of the autoradiographic investigation with the histological and biometric characteristics of the thyroid tissue.

Materials and methods. Thyroidin and methylthiouracil were administered orally in the form of suspensions in 0.5 ml of water with the aid of a metallic catheter. On a background of the continuing administration of the preparations on the 14th day of the experiment the rats received intraabdominally a dose of 10 μCu of I^{131} each in the form of sodium salt without carrier. The animals were killed in periods of from 2 minutes to 21 days after the administration of the radioiodine. The thyroid glands were suspended on torsion balances, fixed in Carnoy's fluid, and covered with paraffin via chloroform. A part of the sections was stained with hematoxylin-eosin. The autoradiography was conducted according to the method of covering with a liquid emulsion (Belanger and Leblond) with the use of an emulsion of type P, diluted twice. In comparing the intensity of the reaction the magnitude of the exposure was taken into account; in addition, preparations of various groups, mounted on a single slide, were compared. The determination of the dimensions of the follicles and the height of the thyroid epithelium was conducted with the aid of an ocularmicrometer via the checking of 100 units of observation in various preparations of each group (all were taken into account without excluding the follicles, located along the short axis of the vertical section through a lobe of the thyroid gland, passing close to the center of the latter).

Results. The histobiometric characteristics of the thyroid tissue are presented in Table 1. Below are set forth the data of the autoradiographic investigation.

Table 1

Biometric Characteristics of Thyroid Glands

	Group of animals						
	First	Second			Third		
	$M \pm E_M$	$M \pm E_M$	Difference from the first group	Error of the Difference	$M \pm E_M$	Difference from the first group	Error of the Difference
Weight of the lobe in mg	14.3 ± 0.3	8.9 ± 0.4	-5.4	0.5	43 ± 2	+28.7	2
Form and dimensions of the follicles in μ		Spherical			Cylindrical		
	$d=38.4 \pm 2$	$d=72.5 \pm 2.5$	+34.1	3.2	$H=75 \pm 3.5$ $d=38 \pm 0.9$	--	--
Height of the epithelium in μ	7.1 ± 0.3	2.8 ± 0.2	-4.3	0.4	12.2 ± 0.2	+5.1	0.4

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First group. The autoradiograms of the thyroid gland two and 10 minutes after the administration of radioactive iodine (exposure two days) present accumulations of individual grains, located above the colloid and apical divisions of the cells (Fig. 1a). An hour after the administration of radioactive iodine (Fig. 1b) in the presence of the same exposure rather intense blackenings are usually detected in the form of closed rings, corresponding to the thyroid follicles. The density of the location of the grains above various segments of the ring may not be identical. After 24 hours (Fig. 1c) the autoradiogram, exposed for the course of two days, displays a sharply positive reaction over a majority of the follicles in the form of continuous blackenings (disks), corresponding to the colloid. The intensity of the reaction over various follicles is different; under these conditions the large peripheral follicles give less dense images. However, even over follicles which are similar in dimensions and position, considerable differences in the density of the location of the granules are observed. Four days after the administration of I^{131} the autoradiographic reaction is rendered somewhat weaker, but in the presence of exposure for the course of seven days it is well expressed (Fig. 1d). Under these conditions the density of the images over the coarse peripheral follicles becomes somewhat greater than over the finer follicles of the rest of the gland. Toward the eleventh day even in the presence of a 14-day exposure the autoradiographic reaction is displayed almost exclusively over the peripheral follicles (Fig. 1e). On the 21st day after the administration of radioactive iodine we did not succeed in detecting it on the autoradiograms. Individual differences between the animals are manifested in intensity, and also in the periods during which one or another reaction arises.

Second group. The autoradiographic study has shown a considerable lowering of the intensity of the reaction at all periods of the investigation: in the presence of the exposure of the preparations for the course of 10-16 days at 10 minutes after the administration of radioactive iodine there was no blackening; after an hour and after 24 hours (Fig. 2a) accumulations of individual granules were observed over the colloid; on the fourth day (Fig. 2b) the image became more intensive, a pronounced positive reaction was also noted 11 days after the administration of radioactive iodine (Fig. 2c). No ring reaction was observed. Differences between the central and peripheral follicles, the dimensions of which became identical, also failed to be noted.

Third group. The autoradiographic reaction was acutely weakened at all periods of the investigation. Even in the presence of a 35-day exposure no images were visible 10 minutes after the administration of radioactive iodine; after an hour isolated granules over the colloid were observed, after 24 hours (Fig. 3a) there were accumulations of grains over many follicles; on the fourth day (Fig. 3b) radioactive iodine was hardly manifested at all.

Discussion. As was shown in the works of Leblond and Gross, Bogoroch and others, when the thyroid gland is treated histologically, the iodine which does not enter into the composition of the protein is washed out from the tissue, while the radioactive iodine remaining in it is bound with the thyreoglobulin. Thus, the substrate of the autoradiographic image in the fixed sections is newly formed thyreoglobulin. Under the same experimental conditions which were used in the present work, in normal rats as soon as two to 10 minutes after the administration of I^{131} the latter can be detected in the thyroid tissue in the composition of the protein compounds, although in small quantities. After an hour the newly formed thyroglobulin is localized basically along the periphery of the follicles, inducing on the autograms a distinct ring reaction. The continuity of these rings is evidence that all the cells of the epithelial lining of the follicles participate in the synthesis of the thyroid hormone, although the degree of their activity can be various; this is indicated by the presence in a dense distribution of granules above various segments of the ring. In every case the views of Langendorff, Hurthle, Florentin and others, according to which the thyroid secretion is effectuated almost exclusively by the so-called colloid cells, constituting the lowest part of the epithelial lining of the follicle, can be rejected on the basis of autoradiographic data.

The study of the organoids of the cell and the intracellular inclusions in the follicular cells by the Bensley method has served as the occasion for notions to the effect that the function of the thyroid follicles proceeds via shifting of the accumulation phase and the phase of incretion of the hormone into the blood (Wahlberg). The opinion has repeatedly been advanced to the effect that under ordinary physiological conditions the formation of the thyroid hormone proceeds only in a small part of the follicles, while the others are found in a state of rest (M. F. Merkulov, Klark and Rul (Clark and Rul), and others). However, in the investigation of autoradiograms under conditions of sufficiently prolonged exposure radioactive iodine can be detected in

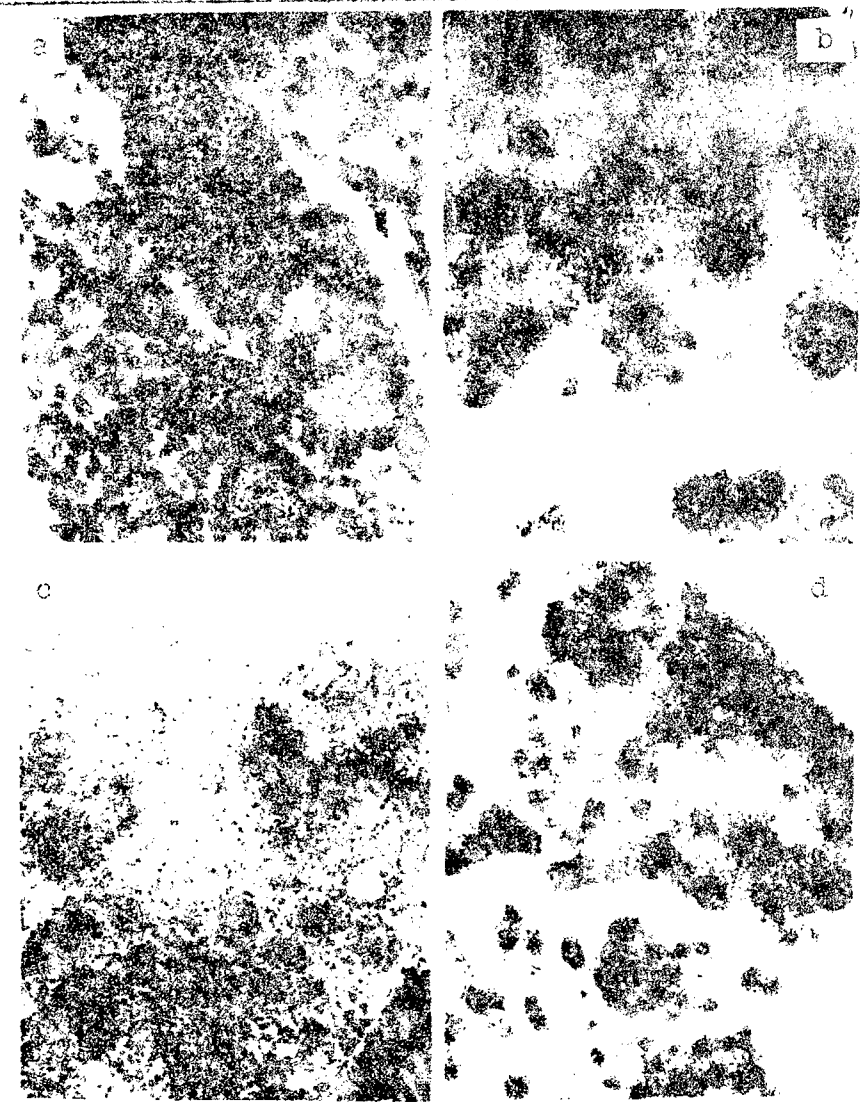
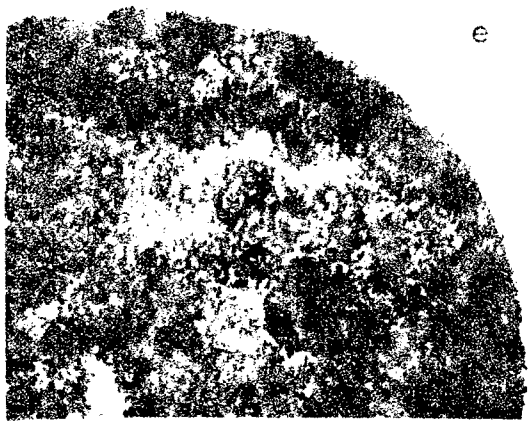


Fig. 1. Autoradiograms of the thyroid glands of rats, killed at various periods after the administration of radioactive iodine.

a -- after 10 minutes. Exposure two days. Objective X 20, Ocular X 10. R (stretching of the bellows) - 40 cm; b -- after an hour. Exposure 2 days. Ob. X 10, oc. X 10, R - 40 cm; c -- after 24 hours. Exposure 2 days. Ob X 10, Oc. X 10, R - 40 cm; d -- after 4 days. Exposure 7 days, Ob. X 10, oc. X 10, R - 35 cm

[Fig. 1 continued on next page]

[Fig. 1 continued from page 6]



e

e -- after 11 days, Exposure 14 days, Ob. X 10, oc. X 10, R - 35 cm.

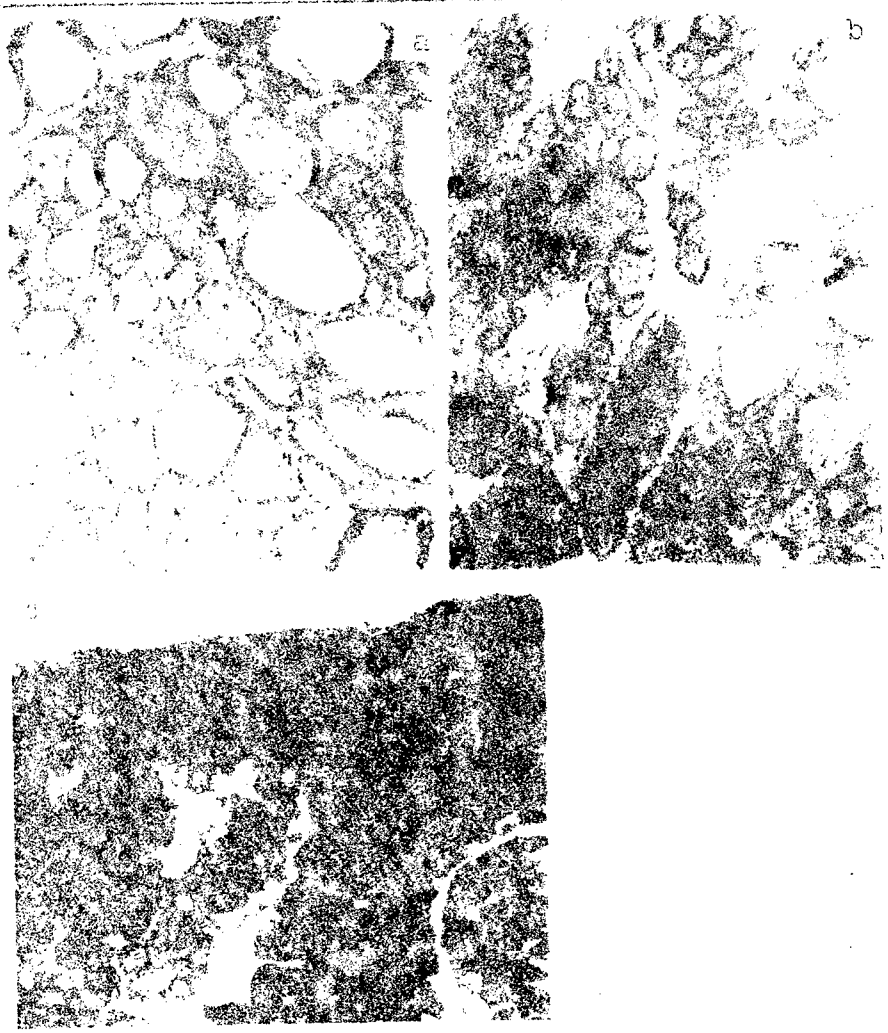


Fig. 2. Autoradiograms of thyroid glands of rats which had received thyroidin.

a -- 24 hours after the administration of radioactive iodine. Exposure 10 days. Ob. X 10, oc. X 10, R -- 40 cm; b -- after 4 days. Exposure 16 days. Ob. X 10, oc. X 7, R -- 40 cm; c -- after 11 days. Exposure 16 days. Ob. X 6, oc. X 7, R -- 40 cm.

all the follicles of the animals killed 10 minutes -- four days after the administration of radioactive iodine. These results contradict the notions of the shifting of the phases of the secretory cycle in the follicle and the alternate functioning of the latter. The most probable explanation of these results is that all the follicles of the thyroid gland in each given moment participate in the synthesis of the thyroid hormone (Leblond and Gross).

Functional differences between the individual follicles consist in the speed of execution of the secretory cycle; thus, the large follicles of the peripheral zone in comparison with the finer central follicles more slowly accumulate and longer retain the proteinbound iodine. A greater biological half-life period is noted in the large follicles by Doniach and Pelc (1949), Nadler and others. Certain differences in the rate of metabolism of iodine are also observed between morpholigically similar follicles.

We have not succeeded in tracing the process of resorption and passage of the accumulated hormone into the cells and blood on the autoradiograms. This is natural, if one takes into account, that the mobilization of the thyroid hormone proceeds via the proteolytic splitting of thyreoglobulin, while the products of hydrolysis (including thyroxin and other iodine containing amino acids) are eliminated from the tissue in the process of histological treatment.

In an experiment with the administration to animals of thyroidin, the autoradiographic investigation shows a lowering of the level of synthesis of protein-bound iodine and a considerable slowing of the rate of its formation and excretion. Under these conditions the ring phenomenon was not observed at any period of the investigation, which is in disagreement with the data of Doniach and Pelc (1949), who noted in an analogous experiment a prolonged retention of protein bound iodine in the cells of the thyroid follicles.

The administration to animals of methylthiouracil led in our experiments to an acute diminution of the quantity of proteinbound iodine in the thyroid tissue at all periods of the investigation with simultaneous acceleration of the process of resorbtion of the accumulated hormone from the cavity of the follicle. The inhibition of the organic binding of iodine appears to be a generally recognized mechanism of antithyroid action of thiourea derivatives (Astwood, Franklin, Chaikoff, and Lerner, Ya. M. Kabak, I. E. Sterin, and others). In the presence of large doses of methylthiouracil one can obtain complete blocking of this process. A. A. Voytkevich expresses an original point of view concerning the mechanisms of the antithyroid action of thiourea: he considers, that an impoverishment of the thyroid gland with

respect to the hormone ensues as a result of the intensified stimulation on the part of the thyrotropic hormone of the hypophysis, while the cause of the thyrotropic stimulation is a disturbance of the utilization of the thyroid hormone in the periphery.

Taking into account that the intensified production of the thyrotropic hormone actually takes place in the presence of the action of methylthiouracil (B. V. Aleshin and N. S. Demidenko, Yu. B. Skebel'skaya, Ye. B. Pavlova, and others), while the weakening of the autoradiographic reaction of the thyroid gland can be associated with an accelerated excretion of organically bound iodine into the blood, we set up a supplementary experiment on six rats, in which a thyrotropic reaction had arisen in the presence of the action of methylthiouracil (80 mg per day) averted via the simultaneous administration of thyroidin (40 mg per day). The autoradiographic investigation showed the complete absence of organically bound iondine in the thyroid gland one, 4, and 11 hours after the administration of the radioactive iodine, although the histological changes, characteristic for the action of methylthiouracil, did not arise under these conditions. The results obtained serve as yet another demonstration of the direct blocking of the process of the organic binding of iodine under the action of thiourea derivatives.

To what degree do the histological and biometric shifts in the thyroid gland under the influence of thyroidin and methylthiouracil reflect changes in the functional activity of the thyroid tissue? The values presented in Table 1 of the individual biometric indexes indicates statistically reliable differences in the histological structure of glands of the first, second, and third groups. The biological meaning of these differences and their connection with thyroid function can be evaluated via the analysis of those stereometric correlations which occur in the follicles of the thyroid gland, with this object we considered a number of summary indexes for the average follicle of each group:
1) the sterometric index of deposition:

$$K_{(\text{small delta})} = \frac{\text{volume of colloid}}{\text{volume of epithelium}} \quad \left(\frac{V_{\text{colloid}}}{V_{\text{epithelium}}} \right);$$

2) the stereometric index of the conditions of resorption of the colloid K_r - $\frac{\text{resorption surface}}{\text{volume of colloid}}$ $\left(\frac{S_p}{V_k} \right)$.

The methods of calculation and the values of these indexes are presented in Table 2.

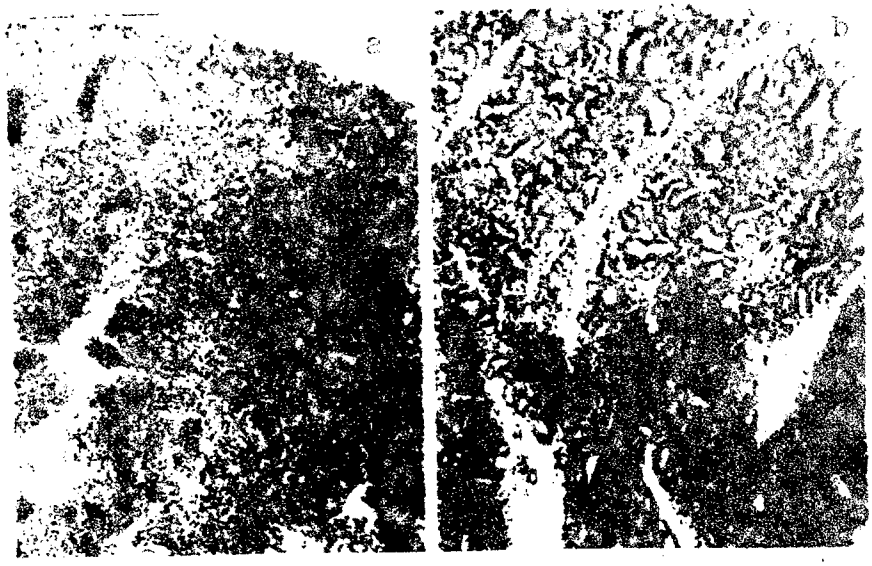


Fig. 3. Autoradiograms of the thyroid glands of rats which had received methyl-thiouracil.

a -- 24 hours after the administration of radioactive iodine. Exposure 35 days. Ob. X 10, oc. X 7, R - 30 cm; b -- after 4 days. Exposure 35 days. Ob. X 10, oc. X 7. R - 35 cm.

Table 2

Stereometric relations in the average follicle

Group	Numerical value of the parameters in u	K small delta = $\frac{V_k}{V_e}$ calculation formula	numerical value
First	D = 38 D_1 = 24	$\frac{D^3}{D3 - D_1^3}$	0.34
Second	D = 72.5 D_1 = 67	$\frac{D_1^3}{D3 - D_1^3}$	5
Third	R = 19 H = 75 R_1 = 7 H_1 = 51	$\frac{R_1^2 H_1}{R^2H - R_1^2 H_1}$	0.1

Conventional symbols: D -- diameter of the spherical follicles of the first and second groups; D_1 -- diameter of the cavity of the follicles of the first and second groups; R and H -- radii of the base and height of the cylindrical follicles of the third group; R_1 and H_1 -- those same parameters for the cavity of the cylindral follicles of the third group.

Table 2 continued from Page 13

$$K_r = \frac{S_r}{V_k}$$

calculation formula	numerical value
$\frac{6}{D_1}$	0.25
$\frac{6}{D_1}$	0.09
$\frac{2(R_1 + H_1)}{R_1 H_1}$	0.32

On the basis of the available data concerning the weight of the thyroid gland (P) and the value of the index K_g an approximate determination of the total volume of the secreting tissue (epithelium) and of the deposited secretion (colloid)[1] was conducted --

$V_{\text{epithelium}} = \frac{P}{K_{\text{small delta}} + 1}$, $V_k = P - V_{\text{epithelium}}$. The results for each group are presented on Fig. 4.

The summary biometric characteristics presented in Table 2 and on Fig. 4, are evidence that under the influence of thyroidin there arises an acute diminution in the volume of the secretory tissue, an increase in the stereometric index of deposition, and a worsening of the stereometric conditions of resorption. Under the action of methylthiouracil the volume of the secretory tissue is considerably increased, the index of deposition is rendered less, and the stereometric conditions of resorption are improved.

The biometric changes in the thyroid gland under the action of thyroidin are in excellent agreement with the autoradiographic data. The diminution in the volume of the secreting tissue, the depression of the hormone formation process and the retardation of the resorption of the secretion constitute a single complex of adaptive changes which induce a lowering in the function of the thyroid gland in response to the introduction of exogenic hormone into the organism.

More complex relationships arise under the action of methylthiouracil. At first glance the results of the biometric investigation, which indicate an activation of the thyroid function, contradict the autoradiography data, which indicate a considerable inhibition of the hormone formation. However, this contradiction is only apparent. For the correct explanation of the experimental facts it is necessary strictly to distinguish the concept of the specific activity of the thyroid gland and the concept of its secretory activity.

The specific activity of the thyroid gland consists in the secretion into the blood of thyroid hormones. The

[1] The following assumptions were made in this situation: 1) the weight of the glands can be equated to the volume, since the correction for the specific weight is insignificant; 2) the ratio of the volumes of the epithelium and the colloid for the gland as a whole corresponds to the ratio of these volumes for the "average" follicle; 3) the stroma of the gland and the vessels occupy a comparatively small volume and we do not have to take them into consideration.

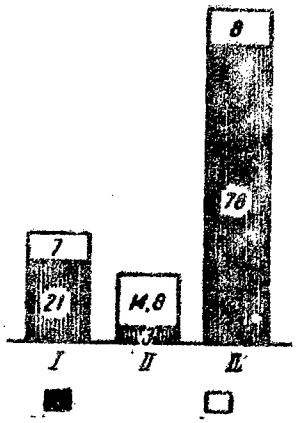


Fig. 4. Ratio of the volume of cells and of colloid in the thyroid gland.

I -- normal rats; II -- rats which had received thyroidin; III -- rats which had received methylthiouracil.

level of the specific function depends on two factors: the quantity of product being secreted and its biological activity. The quantity of product being secreted is determined by the secretory activity of the gland: the mass of secreting tissue, the intensity of the formation and the rate of secretion of the product. The biological activity of the secretion depends on the content in it of iodothyronines in it and is determined by the state of the iodine metabolism.

The disturbance of the process of organic binding of iodine under the action of methylthiouracil leads to a deficit of the thyroid hormone in the organism and to an intensification of the thyrotropic stimulation of the thyroid gland, as a result of which there arises a rise in the secretory activity (an increase in the secreting mass of cells, an acceleration of the secretory cycle), which has the character of a compensatory process.

In taking account of the absence of a direct connection between the iodine metabolism and the secretory activity of the thyroid tissue, it should be underlined that the histobiometric characteristics of the thyroid gland reflect the state of its secretory activity and can be an index of specific function only when the iodine metabolism is undisturbed.

A clear-cut demarcation of the concepts of the specific and the secretory activity of the thyroid tissue poses new questions in the field of the pathology of the thyroid gland.

Conclusions

1. In the normal thyroid gland of rats the formation of the hormone is the result of the simultaneous functioning of all the follicles, which effectuate the synthesis and accumulation of iodothyroglobulin. There are differences between the individual follicles in the intensity and rate of iodine metabolism.

2. Under the action of thyroidin there arises a diminution of the scales and intensity of the hormone formation and a retardation of the secretion of the hormone.

3. Under the action of 6-methylthiouracil there occurs an acute depression of the synthesis of the protein-bound iodine with a compensatory increase in the scales and rate of secretion.

4. The concept of the specific (hormone forming) activity of the thyroid tissue should be distinguished from the concept of its secretory activity, which determines the scale of the synthesis and the rate of the secreting of the

secretion without regard for its physiological quality.

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